(FILE 'HOME' ENTERED AT 13:23:42 ON 09 APR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 13:24:52 ON 09 APR 2003

L1	0	S COW AND OSTEOARTHRITIS AND ATP
L2	10606	S ATP SYNTHESIS
L3	38505	S OSTEOARTHRITIS
L4	5	S L2 AND L3
L5	2	DUP REMOVE L4 (3 DUPLICATES REMOVED)
L6	770	S L2 AND DISEASE?
L7	524	DUP REMOVE L6 (246 DUPLICATES REMOVED)
L8	1	S L7 AND ARTHRITIS
L9	60	S OSTEOARTHRITIS AND MITOCHONDRIA?
L10	46	DUP REMOVE L9 (14 DUPLICATES REMOVED)
L11	7	S L10 AND ATP
L12	10630	S MITOCHONDRIA? FUNCTION
L13	2563	S L12 AND DISEASE
L14	61	S L13 AND DEFECTIVE
L15	5	S L14 AND REVIEW
L16	4	DUP REMOVE L15 (1 DUPLICATE REMOVED)
L17	1060	S L12 AND CELL DEATH
L18	111	S L17 AND REVIEW
L19	4	S L16 AND DEFECTIVE
L20	4	DUP REMOVE L19 (0 DUPLICATES REMOVED)
L21	304	S L17 AND ATP
L22	26	S L17 AND ATP SYNTHESIS
L23	12	DUP REMOVE L22 (14 DUPLICATES REMOVED)
L24	3	S L17 AND (TGF OR TRANSFORMING GROWTH FACTOR)
L25	1	DUP REMOVE L24 (2 DUPLICATES REMOVED)
L26	13	S L12 AND (TGF OR TRANSFORMING GROWTH FACTOR)
L27	6	DUP REMOVE L26 (7 DUPLICATES REMOVED)
L28	492	S L3 AND (TGF OR TRANSFORMING GROWTH FACTOR)
L29	6	S L28 AND MITOCHONDRIA?
L30	3	DUP REMOVE L29 (3 DUPLICATES REMOVED)

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L1	0	S COW AND OSTEOARTHRITIS AND ATP
L2	10606	S ATP SYNTHESIS
L3	38505	S OSTEOARTHRITIS
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L5	2	DUP REMOVE L4 (3 DUPLICATES REMOVED)
L6	770	S L2 AND DISEASE?
L7	524	DUP REMOVE L6 (246 DUPLICATES REMOVED)
L8	1	S L7 AND ARTHRITIS

L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:48763 CAPLUS
DOCUMENT NUMBER: 132:320200
TITLE: Secondary abnormalities of mitochondrial DNA associated with neurodegeneration
AUTHOR(S): Tabrizi, S. J.; Schapira, A. H. V.
CORPORATE SOURCE: University Department of Clinical Neurosciences, Royal Free and University College Medical School, London, NW3 2PF, UK
SOURCE: Biochemical Society Symposia (1999), 66(Mitochondria and Cell Death), 99-110
CODEN: BSSYAT; ISSN: 0067-8694
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review**, with 65 refs. The central nervous system has a particularly high energy requirement, thus making it very susceptible to defects in **mitochondrial function**. A no. of neurodegenerative **diseases**, in particular Parkinson's **disease** (PD), Huntington's **disease** (HD) and Friedreich's ataxia (FRDA), are assocd. with mitochondrial dysfunction. The identification of a mitochondrial complex-I defect in PD provides a link between toxin models of the **disease**, and clues to the pathogenesis of idiopathic PD. The authors have undertaken genomic transplantation studies involving the transfer of mitochondrial DNA (mtDNA) from PD patients with a complex-I defect to a novel nuclear background. Histochem., immunohistochem. and functional anal. of the resulting cybrids all showed a pattern in the PD clones indicative of a mtDNA mutation. There is good evidence for the involvement of **defective** energy metab. and excitotoxicity in the etiol. of HD. The authors, and others, have shown a severe deficiency of complex II/III confined to the striatum that mimics the toxin-induced animal models of HD. There is also a milder defect in complex IV in the caudate. The tricarboxylic acid cycle enzyme aconitase is particularly sensitive to inhibition by peroxynitrite and superoxide radicals. The authors have found this enzyme to be severely decreased in HD caudate, putamen and cortex in a pattern that parallels the severity of neuronal loss seen. The authors propose a scheme for the role of nitric oxide, free radicals and excitotoxicity in the pathogenesis of HD. FRDA is caused by an expanded GAA repeat in intron 1 of the X25 gene encoding a protein called frataxin. Frataxin is widely expressed and is a mitochondrial protein, although its function is unknown. The authors have found abnormal magnetic resonance spectroscopy in the skeletal muscle of FRDA patients, which parallels our biochem. findings of reduced complexes I-III in patients' heart and skeletal muscle. There is also reduced aconitase activity in these areas. Increased iron deposition was seen in patients' tissues in a pattern consistent with a mitochondrial location. The mitochondrial iron accumulation, **defective** respiratory chain activity and aconitase dysfunction suggest that frataxin may be involved in mitochondrial iron regulation. There is also evidence that oxidative stress contributes to cellular toxicity.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS

L11 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:199564 CAPLUS
DOCUMENT NUMBER: 136:338401
TITLE: The mitochondrion in **osteoarthritis**
AUTHOR(S): Terkeltaub, Robert; Johnson, Kristen; Murphy, Anne; Ghosh, Soumitra
CORPORATE SOURCE: Veterans Affairs San Diego Health Care System, University of California, San Diego, CA, 92161, USA
SOURCE: Mitochondrion (2002), 1(4), 301-319
CODEN: MITOCN; ISSN: 1567-7249
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. In a variety of tissues, cumulative oxidative stress, disrupted **mitochondrial** respiration, and **mitochondrial** damage promote aging, cell death, and ultimately, functional failure and degeneration. Because articular cartilage of chondrocytes are highly glycolytic, **mitochondria**- mediated pathogenesis has not been previously applied in models for pathogenesis of **osteoarthritis** (OA), a cartilage degenerative disease that increases markedly in aging. However, chondrocyte **mitochondria** respire in vitro and they demonstrate swelling and changes in no. in situ in the course of OA. Normal chondrocyte **mitochondrial** function is hypothesized to critically support **ATP** (**ATP**) reserves in functional stressed chondrocytes during OA evolution. In this model, disruption of chondrocyte respiration by nitric oxide, a mediator markedly up-regulated in OA cartilage, is centrally involved in chondrocyte functional compromise. Furthermore, **mitochondrial** dysfunction can mediate several specific pathogenic pathways implicated in OA. These include oxidative stress, inadequacy of chondrocyte biosynthetic and growth responses, up-regulated chondrocyte cytokine-induced inflammation and matrix catabolism, increased chondrocyte apoptosis, and pathol. cartilage matrix calcification. In addn., the direct, sublethal impairment of chondrocyte **mitochondrial ATP** synthesis in vitro decreases matrix synthesis and increases matrix calcification ("disease in a dish"). The wt. of evidence reviewed herein strongly supports chondrocyte **mitochondrial** impairment as a mediator of the

23 ANSWER 3 OF 12 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001230758 MEDLINE
DOCUMENT NUMBER: 21210824 PubMed ID: 11299330
TITLE: A transient inhibition of mitochondrial **ATP synthesis** by nitric oxide synthase activation triggered apoptosis in primary cortical neurons.
AUTHOR: Almeida A; Bolanos J P
CORPORATE SOURCE: Unidad de Investigacion, Hospital Universitario de Salamanca, Spain.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (2001 Apr) 77 (2) 676-90. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB In order to investigate the relationship between nitric oxide-mediated regulation of **mitochondrial function** and excitotoxicity, the role of mitochondrial **ATP synthesis** and intracellular redox status on the mode of neuronal **cell death** was studied. Brief (5 min) glutamate (100 microM) receptor stimulation in primary cortical neurons collapsed the mitochondrial membrane potential (psi(m)) and transiently (30 min) inhibited mitochondrial **ATP synthesis**, causing early (1 h) necrosis or delayed (24 h) apoptosis. The transient inhibition of **ATP synthesis** was paralleled to a loss of NADH, which was fully recovered shortly after the insult. In contrast, NADPH and the GSH/GSSG ratio were maintained, but progressively decreased thereafter. Twenty-four hours after glutamate treatment, ATP was depleted, a phenomenon associated with a persistent inhibition of mitochondrial succinate-cytochrome c reductase activity and delayed necrosis. Blockade of either nitric oxide synthase (NOS) activity or the mitochondrial permeability transition (MPT) pore prevented psi(m) collapse, the transient inhibition of mitochondrial **ATP synthesis**, early necrosis and delayed apoptosis. However, blockade of NOS activity, but not the MPT pore, prevented the inhibition of succinate-cytochrome c reductase activity and delayed ATP depletion and necrosis. From these results, we suggest that glutamate receptor-mediated NOS activation would trigger MPT pore opening and transient inhibition of **ATP synthesis** leading to apoptosis in a neuronal subpopulation, whereas other groups of neurons would undergo oxidative stress and persistent inhibition of **ATP synthesis** leading to necrosis.

Katcheves, Konstantina

To: STIC-ILL
Subject: Application serial number: 09/661848

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Tabrizi et al.
Secondary abnormalities of mitochondrial DNA associated with neurodegeneration.
Biochemical Society Symposia (1999), 66 (Mitochondria and Cell Death), 99-110

Terkeltaub et al.
The mitochondrion in osteoarthritis
Mitochondrion (2002), 1(4), 301-319

Thank you.
Tina

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